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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/786,362	06/25/2001	George M. Grass	109904-00028	6261

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EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,362	GRASS ET AL.	
	Examiner	Art Unit	
	Cheyne D Ly	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-18* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *March 14, 2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' arguments filed February 06, 2004 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. Claims 1-17, Specie A (gastrointestinal tract), are examined on the merits.

IDS

3. Documents AA, AB, AN, and AO on the FORM PTO-1449, filed March 14, 2001, have been lined through because said documents have been considered in the FORM PTO-1449, filed June 01, 2001, in the previous Office Action, mailed September 08, 2003.

OATH/DECLARATION

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

5. The Oath, filed June 15, 2001, is defective because of the non-initialed alterations of the last inventor's address have been made to the oath or declaration. See 37 CFR 1.52(c).

CLAIM REJECTIONS - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 3, 4, 7, 8, 12, and 13 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hale et al. (US 5,607,691 A).

8. This rejection is maintained with respect to claims 1, 3, 4, 7, 8, 12, and 13, as recited in the previous office action mailed September 08, 2003.

RESPONSE TO ARGUMENTS

9. Applicant argues Hale et al. does not disclose the limitations of "generating either an in vivo or a stimulated in vitro absorption profile from initial dose data and from in vitro bioavailability data but there is also no mention of using these generated absorption profiles for screening a primary library or portion thereof." Applicant's argument has been fully considered and found to be unpersuasive as discussed below.

10. It is re-iterated that Hale et al. discloses a method for screening a compound library (columns 31-32, vi. Screening Procedures §) by absorption wherein the rate of transdermal pharmaceutical agent absorption is primarily determined by the agent's lipid solubility (column 1, lines 67-68, to column 2, lines 1-16).

11. The properties characterized by human in vivo and in vitro cell based assays include membrane transport rate, delivery rate, serum half-life, and biodistribution, including the enhancement of pharmacokinetic and pharmacodynamic properties, such as lipophilicity and/or solubility, and partition coefficient (column 44, lines 45-67 to column 46, lines 1-24).

12. The method of Hale et al. is directed to screening a "primary library" comprising covalently linked pharmaceutical agent-chemical modifier complexes. "Once the optimal

chemical modifier is identified, the screening procedure can be repeated to further optimize the composition of the pharmaceutical agent (secondary library) (column 31, lines 46-63).

13. Hale et al. discloses the suitable dose for transdermal transport that is therapeutically effective is less than 50 milligrams per day (initial dose) (Claim 1). The method of Hale et al. comprises in vitro testing of pharmaceutical agents wherein the bioavailability data determines further study for improved iontophoretic transdermal deliverability (column 45, lines 12-18). Further, the pharmaceutical agents are tested by in vivo assays wherein absorptions profiles (antibody-mediated reaction, an activity assay,...and monitoring the radioactivity) (column 94, Examples 14 and 15) are determined as part of the method of Hale et al. for selecting enhanced agents for the delivery through membranes (column 2, lines 55-67).

14. The above response to Applicant's argument and the below citation of Hale et al. fully address Applicant's argument. Further, the disclosure of Hale et al. clearly anticipates all the limitations of claims 1, 3, 4, 7, 8, 12, and 13.

REJECTION RE-ITERATED

15. Hale et al. discloses a method for screening a compound library (columns 31-32, vi. Screening Procedures §) by absorption wherein the rate of transdermal pharmaceutical agent absorption is primarily determined by the agent's lipid solubility (column 1, lines 67-68). More specifically, Hale et al. discloses the absorption of agent as directed to the gastrointestinal surfaces (column 1, lines 42-48), as in instant claim 12.

16. "Few pharmaceutical agents fit this profile and those which do are not always predictably absorbed" (column 2, lines 5-7). The recommended administered dosage (initial dose) is less

than 50 mg/day (column 11, lines 45-51). "Typically, this library will be synthesized in a solid-state format with each modifier bound to a substrate via a cleavable linker. The compound can then be cleaved from the substrate and screened in vitro as to their transport or other characteristics." The screening procedure is repeated to optimize for generating the pharmaceutical agent (columns 31-32, Screening Procedures §). The first and secondary libraries are disclosed in Tables 1 and 2 where the compounds are selected, as in instant claim 13.

17. The properties characterized by human in vivo and in vitro cell based assays include membrane transport rate, delivery rate, serum half-life, and biodistribution, including the enhancement of pharmacokinetic and pharmacodynamic properties, such as lipophilicity and/or solubility, and partition coefficient (column 44, lines 45-67 to column 46, lines 1-24), as in instant claims 1, 3, 7, and 8.

18. 5-Fluorouracil is an antineoplastic antimetabolite wherein there is evidence that the metabolism of fluorouracil in the anabolic pathway blocks the methylation reaction of deoxyuridylic acid to thymidylic acid (column 22, lines 33-38), as in instant claim 4.

CLAIM REJECTIONS - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hale et al. (US 5,607,691 A) taken with Yang et al. (1994) in view of Jacobson et al. (US 5,773,423 A).

22. This rejection is maintained with respect to claims 1-17 as recited in the previous office action mailed September 08, 2003.

RESPONSE TO ARGUMENTS

23. Applicant's argument as directed to Hale et al. has been fully considered and found to be unpersuasive as responded to above. Further, the disclosure of Hale et al. has overcome the prior art deficiencies of Yang et al., and Jacobson et al. as argued by Applicant.

REJECTION RE-ITERATED

24. Hale et al. discloses the limitation of claims 1, 3, 4, 7, 8, 12, and 13 as discussed above.

25. However, the method of Hale et al. is not limited to a computer-implemented pharmacokinetic tool or structure relationship information.

26. Jacobson et al. discloses a compound screening procedure (column 8, lines 14-16) for improving pharmacokinetic investigations (column 26, lines 51-52) wherein the biological

activity of compounds are unknown (column 5, lines 29-37), binding assay is used to study structure activity relationship and the method is computer implemented (Example 35, specifically columns 40, lines 59-61 and column 42, lines 10-19), as in instant claims 9-11 and 14.

27. Further, the method of Jacobson et al. comprises statistical error determination and control (column 51, lines 59-61, column 52, lines 5-19, and Figure 2), as in instant claim 6.

28. Yang et al. discloses the pharmacokinetic investigations comprising computer readable components for modeling and simulations requiring data input (pages 63-71). More specifically, the input data is directed to information about dose response and toxicity (page 65, § 3.4.1, lines 5-14), and a graphical profile is generated as an output (Figure 3.8) as in instant claims 2, 5, and 15-17.

29. The method of Yang et al. comprises differential equations requiring physiological parameters, adjustment parameters, and correlation parameters (page 63-65, §3.3.5), as in instant claim 6.

30. Jacobson et al. discloses a compound screening procedure (column 8, lines 14-16) for improving pharmacokinetic investigations (column 26, lines 51-52) and Yang et al. discloses pharmacokinetic investigations comprising computer readable components for modeling and simulations (pages 63-71). While, Hale et al. disclose a method for screening a compound library (columns 31-32, vi. Screening Procedures §) as directed to pharmacokinetic investigations (column 44, lines 45-67 to column 46, lines 1-24). Thus, the improvements suggested by Jacobson et al. are directly applicable to the pharmacokinetic investigations of Hale et al. and Yang et al.

31. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated by Jacobson et al. for improving pharmacokinetic investigations. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the method for screening a compound library as taught by Hale et al. and improve on the concept by performing the computer-implemented method as directed to pharmacokinetic investigations as taught by Yang et al. and Jacobson et al.

CONCLUSION

32. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

33. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

34. This application contains claim 18 drawn to an invention nonelected without traverse, filed February 27, 2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

35. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 193), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 872-9306.

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

37. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

38. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

C. Dune Ly
5/10/04

Ardin H. Marschel 5/14/04
ARDIN H. MARSCHEL
PRIMARY EXAMINER